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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Yousuke Takahama

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EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/889,321

Applicant(s)

TAKAHAMA, YOUSUKE

Examiner

Anne Marie S. Wehbe

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 February 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) 13-19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/2/05 has been entered. Applicant's amendment and response also filed on 2/2/05 has been entered. Claims 1-19 are pending in the instant application. This application contains claims 13-19 drawn to an invention non-elected without traverse in the response received on 11/03/03. Claims 13-19 are therefore withdrawn. Claims 1-12 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Rejections - 35 USC § 112

The rejection of claim 3 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's amendment to claim 3.

The rejection of claim 9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's amendment to the claim.

Claims 9-12 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 lacks antecedent basis for "the foreign gene" in line 4. Claim 9 recites a method of sustaining a gene therapeutic effect caused by a "foreign DNA". Thus, antecedent basis is lacking for "foreign gene".

Claim 10 lacks antecedent basis for "the foreign DNA" in line 2. Claim 10 depends on claim 8, which recites a "foreign gene". Thus, antecedent basis is lacking for "foreign DNA". Claims 11-12 depend on claim 10 and thus are included in this rejection.

Claim Rejections - 35 USC § 103

The rejection of claims 1-12 under 35 U.S.C. 103(a) as being unpatentable over Ilan et al. (1996) J. Clin. Invest., Vol. 98 (11), 2640-2647, in view of DeMatteo et al. (1997) J. Virol., Vol. 71 (7), 5330-5335, and further in view of Bakker et al. (1999) J. Immunol., Vol. 162, 3456-3462, is maintained. Applicant's amendments to the claims and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

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The applicant presents arguments against each of the cited references individually. The applicant argues that Ilan et al. does not render the instant invention obvious because Ilan et al. only teaches the administration of hepatocytes transfected with a foreign gene into the thymus and does not teach or suggest using transfected immature T lymphocytes. The applicant argues that DeMatteo et al. also does not teach the administration of transfected immature T lymphocytes to induce tolerance to foreign DNA. In regards to Bakker et al., the applicant argues that Bakker et al. only teaches transfected T lymphocytes in culture and does not suggest administering them to the thymus to induce tolerance. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the rejection of record is based on the **combined** teachings of Ilan et al. in view of DeMatteo et al. and Bakker et al. The office recognizes that each reference individually does not render the instant invention obvious, however, the office has established that the combined teachings of Ilan et al., DeMatteo et al., and Bakker et al. render the instant invention obvious.

As stated in previous office actions, Ilan et al. was cited for teaching the administration of cells transduced with the recombinant adenovirus (Ilan et al., page 2640). Specifically, the previous office action stated that Ilan et al. teaches that in mammals pretreated by thymic injection of cells infected with recombinant adenovirus encoding a therapeutic gene such as human BUGT1, a second intrahepatic injection of the recombinant adenovirus resulted in sustained gene expression of at least 7 weeks (Ilan et al., page 2640). Ilan et al. further teaches

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that protein other than BUGT1 can be used to generate central tolerance, such as proteins associated with autoimmune disease or allograft rejection (Ilan et al., page 2641, column 1). Thus, Ilan et al. was cited for establishing that cells containing and expressing foreign DNA can be used to induce tolerance against the foreign gene by directly administering the cells to the thymus. The teachings of Ilan et al. were supplemented with the teachings of DeMatteo et al. and Bakker et al. Specifically, DeMatteo et al. was cited to supplement the teaching of Ilan et al., by teaching that adenovirus is capable of infecting fetal T lymphocytes in fetal thymus and further that the transduced fetal T lymphocytes induce tolerance (DeMatteo et al., page 5330, abstract, and Figure 1). It was also noted that DeMatteo et al. teaches that by using a cellular carrier to prevent viral extravasation into the periphery, adverse systemic reactions to adenovirus can be avoided (DeMatteo et al., page 5334, column 2). Thus, DeMatteo et al. supplements the teachings of Ilan et al. by teachings that fetal T lymphocytes already present in the thymus can be transduced to express a foreign gene and that these transduced fetal T lymphocytes induce tolerance. DeMatteo et al. also teaches, as does Ilan et al., that instead of directing administering the foreign gene to the lymphocytes in the thymus, cellular carriers can be used, i.e. transduced cells. Bakker et al. was then cited to further supplement Ilan et al. and DeMatteo et al. by teaching methods of infecting fetal T lymphocytes with recombinant adenovirus *in vitro* in fetal thymic organ culture (Bakker et al., page 3457). Bakker et al. was also cited for teaching that fetal thymocytes infected with adenovirus develop into single positive mature T lymphocytes which ultimately migrate to the periphery (Bakker et al., page 3458, Figure 1, and page 3456).

In addition, the rejection of record provides motivation and a reasonable expectation of success in for combining the teachings of Ilan et al., DeMatteo et al., and Bakker et al. The

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previous office action stated that motivation to substitute fetal T lymphocytes for hepatocytes in the methods of Ilan et al. is provided by all of Ilan et al., DeMatteo et al., and Bakker et al. In the methods of tolerance induction taught by Ilan et al., suppression of mature T cells by antilymphocyte serum was used to prevent reactivity of mature T cells with the adenoviral proteins (Ilan et al., page 2640). DeMatteo et al. also teaches that in adult mice, as opposed to neonatal mice, induction of tolerance by intrathymic administration of adenovirus requires suppression of mature T cells and is further aided by using a cellular carrier to prevent viral extravasation into the periphery (DeMatteo et al., page 5334, column 2). Bakker et al. teaches that fetal thymocytes infected with adenovirus develop into single positive mature T lymphocytes which ultimately migrate to the periphery. In view of the need to suppress mature T cells in order to effectively achieve central tolerance by administering adenoviral infected cells to the thymus as taught by both Ilan et al. and DeMatteo et al., and further in view of the ability of transduced fetal T lymphocytes to not only induce tolerance in the thymus but also to develop into mature T lymphocytes capable of populating the periphery, the skilled artisan would have been motivated to induce tolerance by administering transduced fetal T lymphocytes into the thymus instead of transduced hepatocytes in order to stimulate repopulation of the periphery with mature T lymphocytes. Thus, based on the motivation to introduce fetal T lymphocytes to repopulate mature T lymphocytes in hosts treated with antilymphocyte serum, it would have been *prima facie* obvious to the skilled artisan to substitute fetal T lymphocytes for the hepatocytes in the methods of inducing central tolerance to recombinant adenoviruses and adenoviral encoded foreign proteins taught by Ilan et al. Further, based on the successful infection of fetal T lymphocytes in culture taught by Bakker et al., and the art recognized ability

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of fetal lymphocytes in the thymus to induce tolerance as taught by DeMatteo et al., the skilled artisan would have had a reasonable expectation of success in infecting fetal T lymphocytes with the recombinant therapeutic adenoviruses taught by Ilan et al. and using those infected fetal T lymphocytes to induce central tolerance in adult hosts following intrathymic injection.

After analyzing the references individually, the applicant argues that there is no rational for combining the teachings of the cited references and that it appears that the examiner has used improper hindsight reasoning to make the rejection of record. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Furthermore, the rejection of record clearly sets forth in detail the particular motivation for combining the teachings of cited references, see above and the previous office actions. The applicant is also reminded that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). Thus, the office has properly established obviousness under 35 U.S.C. 103 according to the factual inquiries set forth

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in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Therefore, the rejection of record stands.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'Anne M. Wehbé', with a long horizontal stroke extending to the right.